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Crystal and Molecular Structure of Isomorphous Choiesteryl Chloride and Cholesteryl Bromide†

G. V. VANI

Raman Research Institute, Bangalore 560006, India

and

KALYANI VIJAYAN

Materials Science Division, National Aeronautical Laboratory. Bangalore 560017, India

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Cholesteryl chloride and the isomorphous cholesteryl bromide crystallize in the monoclinic space group P2, with two molecules in the unit cell. The cell dimensions are a = 10.82, b — 7.61, t = 21.46 ± 0.02 A, β = 131.8 ± 1° for the chloride and a = 11.10, b = 7.56, c = 21.83 ± 0.02 A, β = 133.9 ± 1° for the bromide. The crystal structure has been solved by the heavy atom method and refined by least-squares procedure using visually estimated photographic data. The terminal group of atoms C(25), C(26) and C(27) are disordered. The rings A and C in the molecule assume slightly distorted chair conformations. Ring B has a 8β, 9α half-chair conformation and ring D has a 13β, 14α half-chair conformation. The ring junctions B–C and C-D are *trans* whereas the junction A–B is quasi *irons*. The chain at C(17) is in a fully extended configuration.

The crystal packing is smectic-like, with the molecules arranged in distinct layers. The neighboring molecules in a layer are oriented antiparallel to each other. The unit cells of the cholesteryl halides are two molecules thick, one molecule wide and one molecule long. The direction of thickness makes an angle of 35° with the a-axis. The width is at 8° to the b-axis and the length is at 5° to the c-axis. The modified Hodgkin notation is $Ma_{35}b_{8}c_{5}211$.

1 INTRODUCTION

Cholesteryl chloride and isomorphous cholesteryl bromide (Fig. 1) are monotropic cholesterogens belonging to the cholestane groups of steroids. Based on their preliminary X-ray and optical studies in 1933, Bernal and

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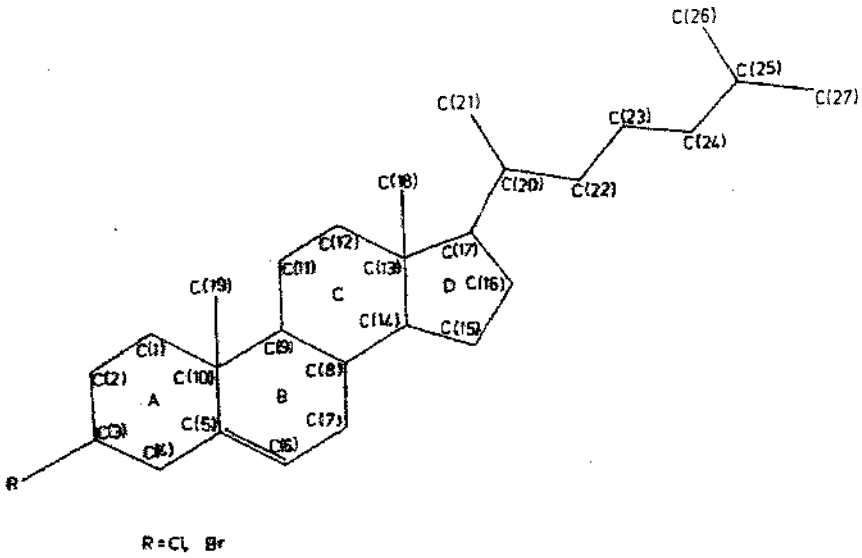

FIGURE I

Crowfoot[1] predicted the orientation of these isomorphous molecules in the unit cell. Later, Bernal *et al.*[2] undertook a slightly more detailed X-ray investigation and worked out the approximate molecular structure as derived from the (hol) Patterson synthesis. In this paper, we report the results of a detailed three-dimensional crystal structure analysis of these compounds, Carlisle and Crowfoot[3] have studied the crystal structures of two forms of cholesteryl iodide, neither of which is isomorphous with cholesteryl chloride and bromide. It turns out however, that the molecular packing in both the forms of cholesteryl iodide is rather different from that in the chloride and bromide. The only other compound forming a cholesteric mesophase whose crystal structurehas been analysed in detail is cholesteryl myristate,[4] but this compound shows a smectic A phase prior to the cholesteric phase. On the other hand, cholesteryl chloride and cholesteryl bromide exhibit only the cholesteric phase and that too only on cooling.

2 EXPERIMENTAL

Crystals of both the compounds, obtained from solutions in acetone, were white, transparent, elongated and platy. From oscillation and Weissenberg photographs the crystals were found to be monoclinic and isomorphous. The

TABLE I

Crystal data

	Cholesteryl chloride $C_{27}H_{45}Cl$	Cholesteryl bromide $C_{27}H_{45}Br$
Molecular weight	405,12	449.57
a	10.82 ± 0.01 A	11.10 ± 0.01 A
b	7.61 ± 0.02 A	7.56 ± 0.02 A
c	21.46 ± 0.01 A	21,83 ± 0.01 A
β	131.8 ± 0.3°	333.9 ± 0.3°
Space group	$P2_1$	$P2_1$
z	2	2
ρ_c	1.02 gm. cm^{-3}	1.13 gm. cm^{-3}
ρ_m	1.03 gm. cm^{-3}	1.14 gm. cm^{-3}

space group was determined as $P2_1$, based on the systematic absenc type oko, k odd. The densities of both the crystals as measured by f in aqueous potassium iodide solution indicated that there are two m per unit cell. The crystal data are listed in Table I.

Three-dimensional intensity data were recorded from the reciproc okl and hKl, K = 0 to 4 for cholesteryl chloride and K = 0 to 3 f< esteryl bromide. Multifilm equi-inclination Weissenberg technique w with copper-Kα radiation. The intensity data of both the crystals poor quality. The diffraction patterns were very weak in intensity an away at relatively low Bragg angles, the highest θ for the observable rei being only 46° for the chloride and 38° for the bromide. The total nu independent reflections observed was 487 and 293 in the two cas responding to only 8 % and 5 % of the total number of possible reflec the respective CuKα spheres.

The intensities were estimated visually and corrected for Loerntz-p tion factors and spot-shape effect. Since the chloride crystals used wer cylindrical, the absorption correction as given by Palm[5] was applied < The bromide crystals used were platy with a rectangular cross-secti the absorption effects were corrected for using the computer pro{ ABSCØR, written by Ramesh Narayan, based on the method of and Levy.[6] The intensity data were scaled to an absolute value using \ statistical method. The overall temperature factors obtained from \ method were 7 and 6 Å^2 for the chloride and bromide structures resp these rather high values are to be expected from the fact that the inten the reflections-*is*^&*dL* away rapidly with increasing θ.

3 STRUCTURE DETERMINATION

The crystal structure was determined by the heavy atom method using the data from the bromide derivative. A three-dimensional bromine-sharpened Patterson map was first computed. The Br–Br vector in the Harker plane could be easily Identified, The refined coordinates of the bromine atom were used to compute a bromine-phased Fourier map and a difference Fourier map. The overall orientation of the molecules as indicated by these maps was parallel to the *c*-axis and compared well with the orientation derived from the Patterson map. Since no satisfactory molecular model could be obtained by placing atoms on the prominent peaks, the occupancy factors of the 49 highest peaks in the bromine-phased Fourier map were refined by least-squares procedure. The refinement indicated that 14 of these positions were likely to be correct. A Fourier map was then computed including contributions from bromine and these 14 carbon atoms. Even though the map was not sufficiently resolved to identify the rest of the atoms unambiguously, a molecular model could be fitted in a unique fashion. Subsequent block-diagonal least-squares calculations proved that this trial molecular model was correct. The model was further refined with both the bromide and the chloride data.

The meagre amount of observed reflections in both the structures led to very poor reflections to parameters ratio. Therefore, while refining the structure, least-squares techniques could not foe totally relied on and Fourier and difference Fourier methods were also coupled with the least-squares procedure. All atoms were corrected for isotropic thermal vibrations. Cruickshank's weighting scheme[7] was used with a — 1.814, $b = -0.014$, $c = 0.001$ for the bromide structure and $a = 0.139$, $b = 0.207$, $c = -0.001$ for the chloride structure. The *R*-factors reduced to 0.183 and 0.22 for the bromide and the chloride structures respectively.

At this stage, the atoms C(25), C(26) and C(27) in the chain at C(17) were found to have strikingly high thermal parameters compared to the rest of the atoms. Also, the molecular dimensions involving these three atoms were very different from the standard values. These disconcerting features suggested the presence of disorder in that part of the molecule. Hence, a difference Fourier map was computed using the data from cholesteryl Chloride after removing the contributions from these three atoms. The difference electron distribution was very diffuse. However, two sets of positions could easily be feeed for each of the three carbon atoms. The occupancy factors of these two sets of positions were refined by the least-squares procedure and were found to be 0.65 and 035 for the original and the new sets of positions respectively.

The difference electron density distribution near the Cl and C(3) positions indicated highly anisotropic thermal vibrations for these atoms and therefore, in the subsequent calculations they were treated for anisotropic thermal motion. At the end of the least-squares refinement which included the disorder of the chain atoms, the *R*-value was 0.18 for the chloride derivative. The molecular dimensions in the disordered region of the molecule had also improved.

The refined coordinates of cholesteryl chloride were used to refine the structure of cholesteryl bromide. Br and C(3) were treated anisotropically. The final *R*-value was 0.155.

The refinement of the anisotropic thermal parameters for the rest of the atoms in the molecule was not undertaken due to the lack of sufficient number of reflections. The scattering factors used were those given by Cromer and Waber.[8]

4 RESULTS AND DISCUSSION

The final positional and thermal parameters of cholesteryl chloride and cholesteryl bromide are listed in Table II.† The thermal parameters in both the structures are high, the average for the carbon atoms being 11.1 $Å^2$ in cholesteryl chloride and 9.1 $Å^2$ in cholesteryl bromide. Due to the paucity of reflections data, the standard deviations of the moelcular dimensions are high. Even though the accuracy of the structure determination is diminished to some extent on account of the large standard deviations of the molecular dimensions, the details of the conformation of the molecule and the molecular packing are not disputable. The lengths of the unsaturated C—C bonds in the steroid nucleus average to 1.55 ± 0.08 A and 1.58 ± 0.17 A in the chloride and the bromide structures respectively. The average values of the valency angles involving sp^3 hybridized carbon atoms in the cyclohexane rings of the chloride and the bromide structures are 110 + 4° and 111 ± 9° respectively. The valency angles in the cyclopentane rings of the two structures average to 102 ± 4° and 104 ± 8° respectively. The molecular dimensions in the terminal chain, particularly in the region beyond the atom C(24) are not reliable because of the disorder. It is interesting to note that high thermal motion in the same region of the molecule has been observed in the crystal structures of cholesterol monohydrate,[9] cholesteryl myristate,[4] cholesteryl *p*-toluene sulphonate[10] and cholesteryl 17-bromoheptadecanoate.[11]

† The tables of structure factors are available with the authors and can be supplied on request.

TABLE II

Final fractional positional coordinates ($\times 10^3$) and thermal parameters. Estimated standard deviations are given in parentheses.

Atom	Cholesteryl chloride				Cholesteryl bromide			
	x	y	z	B(Å²)	x	y	z	B(Å²)
C(1)	727(6)	309(8)	279(3)	12.5(1.5)	727(9)	329(12)	273(4)	8,0(2.4)
C(2)	760(5)	306(6)	354(3)	9,3(1.1)	766(8)	311(12)	355(4)	8.0(2.4)
C(4)	881(6)	−12(8)	392(3)	12.3(1.5)	876(9)	-21(11)	392(4)	8.4(2.5)
C(5)	848(6)	−4(7)	312(3)	10.9(1.3)	838(11)	1(14)	314(6)	12.6(3.2)
C(6)	832(7)	−155(8)	273(3)	12.8(1.5)	841(11)	−150(15)	285(5)	11.8(3.0)
C(7)	816(6)	−175(8)	196(3)	12.8(1.5)	815(10)	-180(13)	204(5)	9.7(2.6)
C(8)	844(4)	−2(6)	170(2)	8.0(1.0)	860(7)	−12(9)	181(3)	2.9(1.7)
C(9)	761(5)	149(7)	184(3)	9.4(1,2)	773(9)	150(18)	188(4)	7.8(2.2)
C(10)	838(5)	171(6)	275(3)	9.6(1.2)	841(7)	175(14)	279(4)	8.7(1.9)
C(11)	776(5)	332(6)	161(3)	9.5(1.1)	759(9)	345(12)	152(5)	7.1(2.4)
C(12)	700(5)	311(7)	65(2)	9.7(1.2)	722(9)	327(13)	65(5)	8.7(2.4)
C(13)	802(5)	174(6)	59(3)	9.5(1.2)	796(8)	158(13)	59(4)	8.5(2.3)
C(14)	761(4)	−1(6)	83(2)	7.7(1.0)	770(10)	−14(13)	88(5)	11.4(3.0)
C(15)	823(6)	−133(8)	55(3)	13.1(1.6)	819(10)	−151(15)	54(5)	10.9(2.9)
C(16)	759(5)	−81(7)	-30(3)	10.0(1.3)	759(10)	−75(14)	−29(5)	9.3(2,6)
C(17)	715(5)	122(7)	-26(2)	9.2(1.1)	702(9)	129(9)	−39(4)	10.7(2.6)
C(18)	983(5)	227(6)	106(2)	9.3(1.1)	981(8)	205(11)	106(4)	6.8(2.2)
C(19)	1015(6)	281(7)	333(3)	11.3(1.3)	1015(9)	260(12)	333(5)	8,8(2.5)
C(20)	746(5)	221(6)	-79(2)	8.7(1.1)	774(11)	202(14)	-71(6)	12.9(3.1)
C(21)	702(6)	418(7)	-92(3)	10.7(1.3)	713(8)	397(12)	−87(4)	7.0(2.2)
C(22)	638(5)	128(8)	−168(3)	11.8(1.4)	657(10)	100(19)	−159(5)	9.5(2.7)
C(23)	692(6)	221(8)	−217(3)	13.0(1.6)	711(13)	150(17)	−208(7)	12.2(4.0)
C(24)	588(6)	114(10)	-305(3)	14.3(1.7)	579(12)	125(20)	−310(6)	10.2(3.3)
C(25)	638(9)	130(13)	350(4)	12.3(2.3)	663(15)			

TABLE II

Final factional positional coordinates ($\times 10^3$) and thermal parameters. Estimated standard deviations are given in parentheses.

Atom	Cholesteryl chloride				Cholesteryl bromide			
	X	Y	Z	B(Å²)	X	Y	Z	B(Å²)
C(1)	727(6)	309(8)	279(3)	12.5(1.5)	727(9)	329(12)	273(4)	8.0(2.4)
C(2)	760(5)	306(6)	354(3)	9,3(1.1)	766(8)	311(12)	355(4)	8.0(2.4)
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C(5)	848(6)	−4(7)	312(3)	10,9(1.3)	838(1!)	1(14)	314(6)	12.6(3.2)
C(6)	832(7)	−155(8)	273(3)	12.8(1.5)	841(11)	−150(15)	285(5)	11.8(3.0)
C(7)	816(6)	−175(8)	196(3)	12.8(1.5)	815(10)	−180(13)	204(5)	9.7(2,6)
C(8)	844(4)	2(6)	170(2)	8.0(1.0)	860(7)	−12(9)	381(3)	2.9(1.7)
C(9)	761(5)	149(7)	184(3)	9.4(1.2)	773(9)	150(18)	188(4)	7.8(2.2)
C(10)	838(5)	171(6)	275(3)	9.6(1.2)	841(7)	175(14)	279(4)	8 7(1 9)
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C(14)	761(4)	−1(6)	83(2)	7.7(1.0)	770(10)	-14(13)	88(5)	11.4(3.0)
C(15)	823(6)	−133(8)	55(3)	13.1(1.6)	819(10)	−151(15)	54(5)	10,9(2,9)
C(16)	759(5)	−81(7)	-30(3)	10.0(1.3)	759(10)	−75(14)	-29(5)	9.3(2.6)
C(17)	7)5(5)	122(7)	-26(2)	9.2(1.1)	702(9)	129(9)	− 39(4)	10.7(2.6)
C(18)	983(5)	227(6)	106(2)	9.3(1.1)	981(8)	205(11)	106(4)	6.8(2.2)

TABLE III

Torsion angles (°)

	Cholesteryl chloride	Cholesteryl bromide
Ring A		
C(10)-C(1)-C(2)-C(3)	−50	-48
C(1)-C(2)-C(3)-C(4)	53	64
C(2)-C(3)-C(4)-C(5)	−47	-56
C(3)-C(4)-C(5)-C(10)	48	54
C(4)-C(5)-C(10)-C(1)	-44	-52
C(2)-C(1)-C(10)-C(5)	43	42
Ring B		
C(10)-C(5)-C(6)-C(7)	5	-12
C(5)-C(6)-C(7)-C(8)	8	25
C(6)-C(7)-C(8)-C(9)	−38	-45
C(7)-C(8)-C(9)-C(10)	62	62
C(8)-C(9)-C(10)-C(5)	−51	−52
C(6)-C(5)-C(10)-C(9)	16	24
Ring C		
C(14)-C(8)-C(9)-C(11)	-62	-52
C(8)-C(9)-C(11)-C(12)	54	37
C(9)-C(11)-C(12)-C(13)	-58	−31
C(11)-C(12)-C(13)-C(14)	63	44
C(12)-C(13)-C(14)-C(8)	-?©	-63
C(9)-C(8)-C(14)-C(13)	69	64
Ring D		
C(17)-C(13)-C(14)-C(15)	53	48
C(13)-C(14)-C(15)-C(16)	-46	-35
C(14)-C(15)-C(16)-C(17)	19	11
C(15)-C(16)-C(17)-C(13)	19	18
C(14)-C(13)-C(17)-C(16)	-46	-41

orsional angles in the various ring systems are listed in Table III. mmetry parameters, ΔC_s and ΔC_2, of Duax and Norton,[12] which te deviation of the conformation of a ring from the ideal conforma- listed in Table IV, Rings *A* and C are in chair conformation with nore distorted than ring *A*, In ring *C*, the mirror plane through the (11)–C(14) is dominant Ring *B* has an 8β,9α half-chair conformation by the double bond between C(5) and C(6). Ring *D* is in 13β, 14α ir conformation. The *A-B* ring junction is quasi-*trans*. The other two ctions, viz., *B*~*C* and *C-D* are *trans*. The side chain at C(17) is in an i conformation. The pseudo-torsion angle C(19)–C(10)···C(13)– 15° in the chloride structure and 11° in the bromide structure. Thus, all apparent twist of the steroid nucleus in these crystal structures is

es 2 and 3 show the packing of the cholesteryl chloride molecules

TABLE IV

Asymmetry Parameters

		Cholesteryl chloride	Cholesteryl bromide
Ring A	$\Delta C_s(1)$	6.7	7.8
	$\Delta C_s(2)$	3.7	12.1
	$\Delta C_s(3)$	3.8	8.1
	$\Delta C_2(1\text{-}2)$	7.6	15.7
	$\Delta C_2(2\text{-}3)$	4.5	9.8
	$\Delta C_2(3\text{-}4)$	5.4	7.8
Ring B	$\Delta C_s(5)$	31.4	19.5
	$\Delta C_s(6)$	15.9	15.4
	$\Delta C_s(7)$	47,3	34.8
	$\Delta C_s(5\text{-}6)$	11.2	5.0
	$\Delta C_2(6\text{-}7)$	44.7	35.4
	$\Delta C_2(7\text{-}8)$	55.6	38.2
Ring C	$\Delta C_s(8)$	10.7	18.2
	$\Delta C_s(9)$	9.0	23.5
	$\Delta C_s(11)$	2.4	5.8
	$\Delta C_2(8\text{-}9)$	13.8	29.5
	$\Delta C_2(9\text{-}11)$	5,3	20.4
	$\Delta C_2(11\text{-}12)$	8.6	9.3
Ring D	$\Delta C_s(13)$	19,2	13.2
	$\Delta C_s(14)$	20.0	23.3
	$\Delta C_s(15)$	54.5	49.3
	$\Delta C_s(16)$	70.1	57.1
	$\Delta C_s(17)$	53.7	44.6
	$AC_2(13\text{-}14)$	0.7	6.5
	$\Delta C_2(14\text{-}15)$	52.1	49.0
	$\Delta C_2(15\text{-}16)$	83.6	72.9
	$\Delta C_2(16\text{-}17)$	83.2	68.9
	$\Delta C_2(17\text{-}13)$	51.1	38.7

in the *ac*- and the *bc*-planes respectively. The unit cell is two molecules thick, one molecule wide and one molecule long, where, as given by Duax and Norton,[12] the length of the steroid is the dimension parallel to the C(10)–C(13) direction, the width is the dimension parallel to the C(12)–C(14) direction and the thickness is the dimension orthogonal to the length and the width. The thickness of the molecule makes an angle of 35° with the fl-axis, the width 8° with the *b*-axis and the length 5° with the *c*-axis. Therefore, the modified Hodgkin notation[12] is $Ma_{35^\circ}b_{8^\circ}c_{5^\circ}$, 211. Similar packing arrangements are frequently observed in steroid structures with two molecules per unit cell.[12]

The molecular arrangement in these structures is interesting. The molecules are stacked in clearly separated layers parallel to the *ab*-plane. The adjacent molecules in a layer are related by the 2, screw axis and are therefore oriented antiparallel to each other. Within each layer, the molecules are tilted

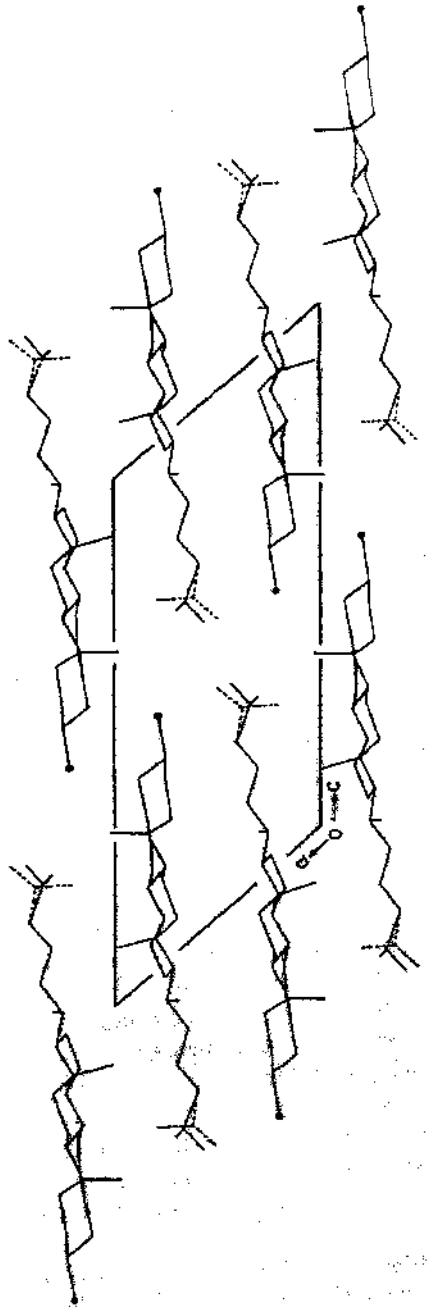

FIGURE 2 Molecular arrangement in the *ac*-plane of cholesteryl chloride.

FIGURE 2 Molecular arrangement in the *ac*-plane of cholesteryl chloride.

respect to the plane normal, giving rise to a smectic C type of packing. As a cholesteric liquid crystal may be looked upon as a twisted nematic, one would expect its crystal structure to have an imbricated molecular arrangement as in the case of a nematogen. The layered arrangement of cholesteryl chloride and cholesteryl bromide seems to suggest that these compounds may have a latent smectic C (or twisted smectic C) phase which does not appear before the compound transforms from the cholesteric phase to the solid phase. This possibility is also supported by the fact that cholesteryl myristate,[4] which has a similar layered arrangement of molecules in the crystalline phase, exhibits a smectic A phase intermediate between its solid and cholesteric phases.

In cholesteryl chloride and cholesteryl bromide, the three dimensional structure is stabilized by nonbonded van der Waal's forces. There are no significantly short intermolecular contacts, implying a rather "loose" packing of the molecules in the unit cell. The only intermoleeular contact distance less than the sum of the van der Waal's radii is due to the introduction of disorder in the chain atoms and is between C(7) of one molecule and C(262) of its neighbour related by the 2_1 screw axis. Each molecule is surrounded by 10 neighbours,

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